

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Effects of omalizumab in severe asthmatics across ages: A real life Italian experience.

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1616930> since 2016-11-28T17:37:07Z

Published version:

DOI:10.1016/j.rmed.2016.09.005

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

Effects of Omalizumab on severe asthma in the elderly: a real life study.

Sposato B¹, Scalese M^{2, 3}, Latorre M, Scichilone N⁴, Matucci A⁵, Milanese M⁶, Masieri S⁷, Rolla G⁸, Steinhilber G⁹, Rosati Y¹⁰, Folletti I¹¹, Baglioni S¹², Bargagli E¹³, Di Tomassi M¹, Pio R¹⁴, Pio A¹⁴, Maccari U¹⁵, Maggiorelli C¹⁵, Migliorini MG¹, Vignale L¹⁶, Pulerà N¹⁷, Carpagnano GE¹⁸, Perrella A^{1, 3}, Paggiaro PL.

¹Pneumologia, Ospedale Misericordia, Grosseto, ²Istituto di Fisiologia Clinica, CNR, Pisa, ³Cardio Thoracic and Vascular Department, Pathophysiology Unit, University of Pisa, ⁴DIMPEFINU, Unit of Pneumology and Medicine, University of Palermo, Palermo, ⁵Immunoallergology Unit, Department of Biomedicine, Policlinico di Careggi, Florence, ⁶Pneumologia, Ospedale S. Corona, Pietra Ligure, ⁷Clinica Otorinolaringoiatrica, Policlinico Umberto I, Università di Roma "Sapienza", ⁸Allergologia e Immunologia Clinica, Ospedale Mauriziano Umberto I, Università di Torino, ⁹Pneumologia Spedali Civili di Brescia, ¹⁰Pneumologia, Ospedale di Macerata, ¹¹Allergologia, Università di Perugia, Az. Ospedaliera Santa Maria, Terni, ¹²Pneumologia, AOU di Perugia, ¹³Pneumologia, Ospedale Le Scotte, Università di Siena, ¹⁴Allergologia e Immunologia Clinica, Mercato S. Severino, Salerno, ¹⁵Pneumologia e UTIP, Ospedale "S. Donato", Arezzo, ¹⁶Pneumologia, Ospedale di Fivizzano, ¹⁷Pneumologia, Ospedale di Livorno, ¹⁸Institute of Respiratory Disease, Department of Medical and Occupational Sciences, University of Foggia, Italy.

Running Head: Omalizumab and elderly severe asthma

Total number pages: 14; Total text word count: 2,758; one table; Abstract word count 305

***Corresponding Author:**

Dr Bruno Sposato

U.O. Pneumologia, Azienda Ospedaliera "Misericordia"

Via Senese 161; 58100 GROSSETO, Italy

Tel. +390564485454 – Fax. +390564485450;

e-mail: bsposat@tin.it

Abstract

Background Asthma in the elderly seems to be more severe compared to asthma in younger patients, with a possible reduced responsiveness to treatment. The aim of this study was to evaluate long-term effects of Omalizumab in elderly asthmatics in a real-life setting.

Methods: 105 consecutive severe asthmatics (step 4-5 according to GINA criteria; mean FEV_1 : $66 \pm 15.7\%$) on treatment with Omalizumab for at least 1 year (mean 35.1 ± 21.7 months) were included into the study and divided into 3 groups according to the age at the onset of Omalizumab treatment: 18-39, 40-64 and ≥ 65 years.

Results: Older subjects differed from the other groups for number of comorbidities, prevalence of overweight/obese subjects and for later asthma onset. A significant and similar reduction of controller therapy and use of SABA on demand was observed in the three groups during omalizumab therapy. FEV_1 increased significantly and similarly in all the groups. Asthma Control Test (ACT) improved significantly ($p < 0.001$) in the three groups, increasing from 15 [12-18] to 24 [22-25] in the younger, from 14 [10-16] to 21 [20-23] in the 40-64 years group and from 15 [12-16] to 20 [18-22] in the elderly, the improvement being lesser than in the other groups ($p = 0.039$). The decrease in asthma exacerbation was significant in all the groups, but the percentage of patients free of exacerbations was higher in the younger (76.9%) compared to middle aged patients (49.2%) and elderly (29%) ($p=0.049$).

Conclusion: Omalizumab improved all asthma outcomes independently of age, but the magnitude of the effects observed in the elderly were significantly lesser than in the other age groups.

Introduction

Severe asthma is defined as the requirement for high-intensity treatment to obtain a disease control (1). However, despite using high doses of inhaled corticosteroids (ICS), bronchodilators and anti-leukotriens, we sometimes fail to achieve asthma control. In this case, adding Omalizumab to treatment permits us to improve the disease control. In fact, Omalizumab (Xolair®) is a recombinant DNA-derived humanized monoclonal antibody indicated as an add-on therapy in patients aged ≥ 6 years with severe persistent allergic asthma uncontrolled at treatment step 4 or 5 according to guidelines GINA (2). Omalizumab demonstrated to be efficacious both in adults and children (3-5). In particular, in real-life studies, anti-IgE therapy showed short- and long-term

benefits in terms of improving lung function and quality of life, achieving asthma control and reducing symptomatology, severe exacerbations, healthcare resource utilizations, hospitalizations, emergency department visits and reducing or discontinuing other asthma medications thus confirming, complementing, and extending evidence from randomized trials (3,5).

However, in the various studies performed to test the effectiveness of Omalizumab, elderly patients are under-represented. Therefore, it is not well clear if Omalizumab is able to improve significantly asthma control in severe asthmatics older than 65 years. Only one study observed an improvement of asthma outcomes after a short follow-up (4 months) of Omalizumab treatment in asthmatics older than 50 years similarly to patients younger than 50 years (6). However, the doubt about Omalizumab effectiveness in patients older than 65 years, above all in the long term, still remains. In fact, there are data suggesting that asthma in older adults is phenotypically different from asthma in younger patients. Some pathophysiological mechanisms of elderly asthma are different from those seen in young asthmatics and these differences may influence the clinical course, asthma outcomes and treatment response in this population. In fact, the elderly have lower post-bronchodilator FEV₁%, more exacerbations and risk of first severe exacerbation is increased by 55.3% when compared to younger patients (7). Asthma in the elderly seems to represent a specific phenotype characterized by more severe, but often less perceived, airway obstruction, a neutrophilic or mixed-type of airway inflammation and frequent comorbidities (8,9). Older asthmatics are often characterized by long-standing asthma that has more severe airflow limitation and less complete reversibility (or even irreversibility) than in patients with late-onset asthma (10). In fact, airways remodeling and a possible coexisting COPD can determine a greater asthma severity in the elderly (11). Older patients with asthma have significantly increased percentages of sputum neutrophils (12). This pattern is a characteristic of intrinsic asthma with neutrophilic inflammation that may be associated to a more severe obstructive disease and a poor response to treatment (8-10). In addition, elderly subjects usually have multiple chronic illnesses that can be also associated with poor asthma outcomes (13-15). Therefore, severe asthma in the elderly may be more serious and thus more difficult to treat in comparison to severe asthma in younger patients. Likely, the advanced age itself may also influence the response to Omalizumab.

Therefore, the aim of this study was to assess the effectiveness of long-term Omalizumab treatment in a real-life setting in patients over 65 with severe uncontrolled asthma.

Materials and Methods

Eighteen Italian Asthma Units were involved in this retrospective study. Data of at least 3 consecutive severe asthmatics (step 4-5 according to GINA criteria) (2) in treatment with Omalizumab, for at least 1 year, were requested from each Center. All recruited patients should have shown a poor disease control with an ICS therapy associated to long-acting bronchodilators and Montelukast for which it was necessary to add Omalizumab. Data were extracted from each patient's clinical record and recorded in a previously agreed form. Information relative to demographic data, allergic sensitization (*Dermatofagoides pteronissinus* and *D. farinae*, Grass mix, *Parietaria*, *Olea europaea*, *Cupressus sempervirens*, *Betula pendula*, *Alternaria tenuis*, *Aspergillus f.* and dog-cat dander), IgE values, the presence of rhinitis, sinusitis, nasal polyposis, other comorbidities (hypertension, chronic heart disease, diabetes, osteoporosis, gastro-esophageal reflux, COPD, obesity), smoking habits and body mass index (BMI) obtained before the onset of Omalizumab treatment were required for each patient. Furthermore, age of asthma onset, Omalizumab dosing and period of treatment with anti-IgE were required in the form. For the purpose of the study, the evaluation, before and after Omalizumab treatment, of FEV₁, FEV₁/FVC, Asthma Control Test (ACT), number of moderate/severe exacerbations registered in the previous year, ICS doses, treatments with LABA, LAMA, Montelukast and how many times a week SABA (as rescue medication) was used, were also considered. It was also evaluated if the treatment was in general stable or reduced after using Omalizumab. The period of data collection was November 2014 – November 2015. At the end of such period, 105 severe asthmatics were recruited.

For the objective of our study, these patients were divided into 3 groups on the basis of age observed at the onset of Omalizumab treatment: subjects aged 18-39, 40-64 and ≥65 years. Then all data of each group were compared.

Exacerbations that required systemic corticosteroids for at least 3 days and/or hospitalizations were taken into account. Obesity was defined by a BMI > 30. The use of ICS with daily dosage was expressed as low (≤500 µg), medium (500-1000 µg) or high (≥1000 µg) dosage of beclomethasone dipropionate, CFC or equivalent according to GINA classification (2). The number of exacerbations and daily dosage of ICS reported in the year before using Omalizumab and during the last year of treatment with anti-IgE (before our study) were considered. The use of SABA (number of times a week) in the month before starting Omalizumab and before the beginning of this study was also taken into account. As regards comorbidities, only those which had a documented evidence were considered. Diagnosis of asthma-COPD overlap was established when, in presence of chronic

cough/phlegm and smoking history, hyperinflation and reduced single breath CO diffusion test (DLCO) <80% was assessed by spirometry and/or central-panlobular emphysema was seen by high resolution computed tomography.

Statistical Analysis

Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile [IQR] range. Categorical variables were expressed as number of cases and percentages.

Comparison of continuous variables among the age groups was performed by using the Kruskal–Wallis test. The Wilcoxon signed-rank test was used to assess the difference between "before" and "after" treatment. The categorical variable frequencies were compared by chi-square test or Fisher's exact test, as appropriate. A logistic binary regression model, corrected for sex, BMI, FEV₁, sensitizations, IgE value, comorbidities, smoking, age of asthma onset, Omalizumab treatment duration, daily dose of ICS and montelukast use, was applied with the purpose to test if zero setting of exacerbations was an independent and different risk factor in the various age brackets (18-39,40-64 and ≥65 years). Furthermore, a linear regression model, corrected for all parameters, above reported, was also performed to test if ACT changes after Omalizumab treatment were independently related to the three classes of age considered (18-39,40-64 and ≥65 years).

All calculations were done by using SPSS software. A $p < 0.05$ was considered as significant.

Results

Asthmatics aged between 18 and 39 years were 13 (12.4% of all patients; mean FEV₁: 67.2±12.4%), whereas patients aged between 40 and 64 years were 61 (58.1% of all patients; mean FEV₁: 65.6±16%) and those aged ≥65 years were 31 (29.5% of all patients; mean FEV₁: 66.2±16.7%). In Table 1, are reported and compared data observed in the three groups with different ages. BMI resulted higher ($p=0.049$) in subjects with medium and older age. No difference in number of allergen sensitizations was found in three groups. Furthermore, no differences were observed in total IgE values (evaluated before beginning the Omalizumab therapy), doses and time (months) of

anti-IgE drug treatment. Also the number of subjects in treatment with ICS, long-acting bronchodilators and montelukast (used before adding Omalizumab) was similar in the three groups. Anyhow, the number of asthmatics with more comorbidities was obviously higher in those with older age.

In figure 1 are reported median FEV₁% values measured before (pre) and after (post) adding Omalizumab. Percentage pre-values (70 [60-76.6]; 68 [55-75]; 67 [58-79]; p=0.838; figure 1/A) and post-values (82.1 [73-88]; 82 [66-93]; 80 [71-92]; p=0.906; figure 1/B) measured in asthmatics with younger, medium and older age (respectively) were similar. Whereas, FEV₁ values, measured after treatment with Omalizumab, improved significantly (p<0.001; comparing pre-post) and similarly in each group. Also ACT values (figure 2), measured after Omalizumab treatment, improved significantly (p<0.001; comparing pre-post – figure 2 A and B) in each group (pre values: 15 [12-18]; 14 [10-16]; 15 [12-16]; post-values: 24 [22-25]; 21 [20-23]; 20 [18-22]; measured in subjects with younger, medium and older age respectively). However, the improvement of ACT observed after Omalizumab was lower in asthmatics over 65 years (20 [18-22]) when compared with younger subjects aged 18-39 years (24 [22-25]; p=0.039; figure 2).

There was a significant reduction in the number of exacerbations after Omalizumab treatment in each group (Figure 3; p<0.0001). The number of exacerbations recorded before the anti-IgE treatment was similar in the three groups, but different after Omalizumab treatment. In fact, no exacerbations were obtained in 76.9% of younger subjects, in 49.2% of patients with medium age and only in 29% of older asthmatics (p=0.049). ICS doses decreased significantly and similarly after anti-IgE treatment in each group (p<0.01; figure 3). We also observed a significant and similar reduction of SABA used as a rescue medication in all groups (Figure 4).

Having found a difference in number of exacerbations among 3 groups, we applied a logistic model considering as dependent variable zero setting of exacerbations corrected for sex, BMI, FEV₁, sensitizations, IgE value, comorbidities, smoking habits, age of asthma onset, Omalizumab treatment duration, daily doses of ICS and montelukast use. Younger subjects showed a significantly higher odd ratios to develop zero exacerbations (subjects aged 40-64: 3.52 [1.21-10.23], p=0.021; subjects aged 18-39: 7.52 [1.47-38.39], p=0.015) in comparison to subjects over 65 years. In addition, having found a lower ACT increase in the elderly, we applied a linear regression model (corrected for all the above said variables) to evaluate the relationship among the three different classes of age and the change of ACT obtained after Omalizumab. In

confirmation to what observed above, we found a significantly reduced increase of ACT (-1.070; $p=0.046$) passing from one class of age to the other, independently of all the confounding variables.

Discussion

According to our long-term real-life study, Omalizumab has demonstrated to be efficient in improving asthma outcomes in all age brackets of uncontrolled severe asthmatics. In fact, FEV₁ and ACT increased whereas, exacerbations, ICS dosage and SABA used as rescue medications decreased significantly after approximately a 3-year Omalizumab treatment in all groups, independently of age.

However, a reduced improvement in ACT and a lower rate of asthmatics without exacerbations in the previous year were found in elderly asthmatics, when compared to younger patients, after a long-term treatment with Omalizumab. In addition, a previous real-life study found that 24% of asthmatics patients in treatment with Omalizumab showed a poor asthma control (16). These subjects were older when compared to well-controlled asthmatics, confirming that just the elderly may have a more difficult control of the disease even with Omalizumab. This would suggest a reduced response to treatment in elderly patients or a more severe asthma more difficult to treat in these categories of subjects. There is no clear evidence supporting a lower efficacy of asthma therapies in older subjects (7,17), whereas it is more probable that a poor response may depend on a different asthma phenotype in the elderly, characterized by a greater disease severity. In fact, according to our study, asthmatics over 65 years, showed a higher BMI (more numerous overweight/obese subjects), a greater number of comorbidities and a more advanced asthma onset age, when compared to younger subjects. These different characteristics may increase disease severity and therefore reduce the response to treatment in the elderly. In fact, overweight/obese status, with an increased subcutaneous and visceral abdominal fat mass, which is a characteristics of elderly subjects, is a risk factor for a higher airway hyperresponsiveness (AHR), lung function decline and risk of asthma (18-24). Furthermore, in obesity, lung volume and tidal volume are reduced, thus promoting airway narrowing (20,24,25). Obesity also leads to a state of low-grade systemic inflammation (increased leptin, TNF- α , IL-6, TGF- β 1, adiponectin and C-reactive protein) that may act on the lungs to aggravate asthma (24,25). In fact, the proportion of obese subjects increased with asthma severity step, reaching the peak in the highest asthma severity step (26). Furthermore, several studies showed an inverse relationship between BMI

categories and reduction in asthma control, in response to all controller therapies (ICS, antileukotrienes and ICS plus long-acting β agonist in combination) (25-29). Therefore, obesity can be an important factor that may have influenced the reduced response to Omalizumab in the elderly asthmatics of our study in terms of ACT level and number of exacerbations.

In addition, overweight and obesity are associated to other comorbidities (glucose intolerance, dyslipidemia, hypertension, type 2 diabetes, kidney failure, osteoarthritis, others) which can lead, in general, to further morbidity and mortality (30). The comorbidity burden is significantly associated with asthma-related quality of life, unscheduled asthma care, emergency department visit, asthma hospitalization, or the 30-day fatality rate following asthma hospitalization (15). Furthermore, comorbidities are associated with an ageing population; they negatively affect health outcomes and are associated with asthma in these subjects (8-10). In fact, according to our study, comorbidities such as hypertension, chronic heart disease, diabetes, gastro-esophageal reflux and osteoporosis are more prevalent in old age, making the disease more severe thus influencing the reduced response to treatment with Omalizumab in the elderly. In confirmation, some researches have shown that poor asthma control, measured as reduced ACT, was associated with asthma-related comorbid diseases in real-life (13,16,31).

In particular, we observed an increased number of elderly subjects affected by hypertension that may be a marker of asthma severity in older asthmatic patients. In fact, according to recent studies (32), asthmatic subjects with comorbid hypertension display evidence of enhanced asthma morbidity.

Another aspect of our study is the proof that asthma onset age was higher in older subjects and that it may have induced the lower efficacy of Omalizumab. Asthma onset age is used to distinguish different adult asthma phenotypes. Asthma starting in adulthood differs from childhood-onset as regards asthma high symptom scores, poor quality of life, the need for high-intensity treatment, low/fixed lung function and high exacerbation rate. Furthermore, patients with severe adult-onset asthma are more often females, non-atopic, with more nasal symptoms, nasal polyposis, higher exhaled nitric oxide levels, blood neutrophil counts and sputum eosinophilia (33,34). All these features, different in younger subjects, may explain the reduced effect of Omalizumab in the elderly. Actually, the development of late-onset adult asthma may be also the clinical consequence of immunosenescence that would lead to decline in functionality of the immune system with increasing age (35-38). This age-related process determines a progressive

impaired mucociliary clearance, changes in airway neutrophil, eosinophil, and mast cell numbers and function over an altered antigen presentation and decreased specific antibody responses (37). Furthermore, this immunosenescence and its associated chronic low grade systemic "inflamm-aging" may contribute to the development and progression of pulmonary disease in older individuals (34,37). Therefore, immunosenescence may favor a neutrophilic inflammation that determines a more severe disease and less effective asthma treatments in the elderly (38). In our study, we found that aging was negatively related to Omalizumab treatment response in terms of increase in ACT and reduction of exacerbations after therapy, independently to all confounder factors considered by this study: sex, BMI, FEV₁, sensitizations, IgE value, comorbidities, smoking habits, age of asthma onset, Omalizumab treatment duration, daily doses of ICS and montelukast use. This suggest that a reduced response to treatment in the elderly may be simply due to a "senescence process" progressing with aging, independently of other factors, that favour a more severe asthma development through an immunological/inflammatory process different from the one seen in younger asthmatics. Therefore, comorbidities may be part of a global "senescence process" together with other pulmonary diseases. According to this concept, comorbidity and asthma should only be associated as one is not the cause of the other.

In conclusion, adding Omalizumab can improve uncontrolled step-4/5 asthma in a real-life setting independently of age. However, improvement may be lower in the elderly. This poorer response to Omalizumab treatment may be due to an association with comorbidities, in particular hypertension and overweight/obese status, and to a more advanced asthma onset age. On the other hand, just the "senescence process" (progressive with age) may be responsible for the lower efficacy of Omalizumab in the elderly.

References

1. Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, Casale TB, Chanez P, Enright PL, Gibson PG, de Jongste JC, Kerstjens HA, Lazarus SC, Levy ML, O'Byrne PM, Partridge MR, Pavord ID, Sears MR, Sterk PJ, Stoloff SW, Szeffler SJ, Sullivan SD, Thomas MD, Wenzel SE, Reddel HK. A new perspective on concepts of asthma severity and control. *Eur Respir J*. 2008 Sep;32(3):545-54.
2. Global Initiative for Asthma. Global Strategy for asthma management and prevention 2012 update. Available at, http://www.ginasthma.org/pdf/GINA_Report_2012.pdf [accessed February 2014].

3. Abraham I, Alhossan A, Lee CS, Kutbi H, MacDonald K. "Real-life" effectiveness studies of omalizumab in adult patients with severe allergic asthma: systematic review. *Allergy* 2015 Dec 8. doi: 10.1111/all.12815. [Epub ahead of print].
4. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, Gruchalla RS, Kattan M, Teach SJ, Pongratic JA, Chmiel JF, Steinbach SF, Calatroni A, Togias A, Thompson KM, Szeffler SJ, Sorkness CA. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med* 2011; 364(11): 1005-15.
5. Caminati M, Senna G, Guerriero M, Dama AR, Chieco-Bianchi F, Stefanizzi G, Montagni M, Ridolo E. Omalizumab for severe allergic asthma in clinical trials and real-life studies: what we know and what we should address. *Pulm Pharmacol Ther* 2015; 31:28-35.
6. Korn S, Schumann C, Kropf C, Stoiber K, Thielen A, Taube C, Buhl R. Effectiveness of omalizumab in patients 50 years and older with severe persistent allergic asthma. *Ann Allergy Asthma Immunol* 2010; 105(4): 313-9.
7. Haughney J, Aubier M, Jorgensen L, Ostinelli J, Selroos O, van Schayck CP, Buhl R. Comparing asthma treatment in elderly versus younger patients. *Respir Med* 2011; 105:838-45.
8. Yáñez A, Cho SH, Soriano JB, Rosenwasser LJ, Rodrigo GJ, Rabe KF, Peters S, Niimi A, Ledford DK, Katial R, Fabbri LM, Celedón JC, Canonica GW, Busse P, Boulet LP, Baena-Cagnani CE, Hamid Q, Bachert C, Pawankar R, Holgate ST. Asthma in the elderly: what we know and what we have yet to know. *World Allergy Organ J.* 2014 May 30;7(1):8.
9. Robitaille C, Boulet LP. Asthma in the elderly. *Rev Mal Respir* 2014; 31(6):478-87.
10. Hanania NA, King MJ, Braman SS, Saltoun C, Wise RA, Enright P et al. Asthma in the elderly Current understanding and future research needs--a report of a National Institute on Aging (NIA) workshop. *J Allergy Clin Immunol* 2011; 128(3 Suppl):S4-S24.
11. Reed CE. Asthma in the elderly: diagnosis and management. *J Allergy Clin Immunol* 2010;126: 681-7.
12. Nyenhuis SM, Schwantes EA, Evans MD, Mathur SK. Airway neutrophil inflammatory phenotype in older subjects with asthma. *J Allergy Clin Immunol* 2010;125 :1163-5.
13. Corrado A, Renda T, Polese G, Rossi A; SERENA (Studio osservazionale per il monitoraggio dell'asma non controllato)/ AIPO Study Group. Assessment of asthma control: The SERENA study, *Respiratory Medicine* 2013; 107(11): 1659-66.

14. Milanese M, Di Marco F, Corsico AG, Rolla G, Sposato B, Chieco-Bianchi F, et al, ELSA Study Group. Asthma control in elderly asthmatics. An Italian observational study. *Respir Med* 2014; 108(8): 1091-9.
15. Song WJ, Cho SH. Challenges in the Management of Asthma in the Elderly. *Allergy Asthma Immunol Res*. 2015 September;7(5):431-439.
16. Novelli F, Latorre M, Vergura L, Caiaffa MF, Camiciottoli G, Guarnieri G, Matucci A, Macchia L, Vianello A, Vultaggio A, Celi A, Cazzola M, Paggiaro P; Xolair Italian Study Group. Asthma control in severe asthmatics under treatment with omalizumab: a cross-sectional observational study in Italy. *Pum Pharmacol Ther* 2015; 31:123-9.
17. Melani AS. Management of asthma in the elderly patient. *Clin Interv Aging* 2013; 8: 913-22.
18. Sposato B, Scalese M. Can overweight/obesity and smoking have combined effects on bronchial hyperresponsiveness. *Eur Respir J* 2014; 43(2): 651-3.
19. Kwon JW, Kim SH, Kim TB, Kim SH, Park HW, Chang YS, et al. Airway hyperresponsiveness is negatively associated with obesity or overweight status in patients with asthma. *Int Arch Allergy Immunol* 2012; 159(2):187-93.
20. Shore SA. Obesity, airway hyperresponsiveness and inflammation. *J Appl Physiol* 2010; 108(3): 735-3.
21. Rossi A, Fantin F, Di Francesco V, Guariento S, Giuliano K, Fontana G, et al. Body composition and pulmonary function in the elderly: a 7-year longitudinal study. *Int J Obes (Lond)* 2008; 32(9): 1423-30.
22. Song WJ, Kim SH, Lim S, Park YJ, Kim MH, Lee SM, et al. Association between obesity and asthma in the elderly population: potential roles of abdominal subcutaneous adiposity and sarcopenia. *Ann Allergy Asthma Immunol* 2012; 109(4): 243-8.
23. Kim KM, Kim SS, Kwon JW, Jung JW, Kim TW, Lee SH, et al. Association between subcutaneous abdominal fat and airway hyperresponsiveness. *Allergy Asthma Proc* 2011; 32(1): 68-73.
24. Shore SA. Obesity and asthma: possible mechanisms. *J Allergy Clin Immunol* 2008; 121: 1087-93.
25. Sutherland ER. Linking obesity and asthma. *Ann N Y Acad Sci*. 2014 Apr;1311:31-41.
26. Teodorescu M, Polomis DA, Gangnon RE, Consens FB, Chervin RD, Teodorescu MC. Sleep duration, asthma and obesity. *J Asthma*. 2013 Nov;50(9):945-53.

27. Peters-Golden M, Swern A, Bird SS, Hustad CM, Grant E, Edelman JM. Influence of body mass index on the response to asthma controller agents. *Eur Respir J*. 2006 Mar;27(3):495-503.
28. Boulet, L. & E. Franssen. 2007. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. *Respir. Med*. 101: 2240–2247.
29. Camargo CA Jr, Boulet LP, Sutherland ER, Busse WW, Yancey SW, Emmett AH, Ortega HG, Ferro TJ. Body mass index and response to asthma therapy: fluticasone propionate/salmeterol versus montelukast. *J Asthma*. 2010 Feb;47(1):76-82.
30. Martin-Rodriguez E, Guillen-Grima F, Martí A, Brugos-Larumbe A. Comorbidity associated with obesity in a large population: The APNA study. *Obes Res Clin Pract*. 2015 Sep-Oct;9(5):435-47.
31. Yildiz F. Factors influencing asthma control: results of a real-life prospective observational asthma inhaler treatment (ASIT) study. *J Asthma Allergy* 2013;6 93-101.
32. Christiansen SC, Schatz M, Yang SJ, Ngor E, Chen W, Zuraw BL. Hypertension and asthma: a comorbid relationship. *J Allergy Clin Immunol Pract*. 2016 Jan-Feb;4(1):76-81.
33. Amelink M, de Groot JC, de Nijs SB, Lutter R, Zwinderman AH, Sterk PJ, ten Brinke A, Bel EH. Severe adult-onset: a distinct phenotype. *J Allergy Clin Immunol* 2013;132(2):336-41.
34. de Carvalho-Pinto RM, Cukier A, Angelini L, Antonangelo L, Mauad T, Dolhnikoff M, Rabe KF, Stelmach R. Clinical characteristics and possible phenotypes of an adult severe asthma population. *Respir Med* 2012;106(1):47-56.
35. Zuo L, Pannell BK, Liu Z. Characterization and redox mechanism of asthma in the elderly. [Oncotarget](https://doi.org/10.18632/oncotarget.7075). 2016 Jan 29. doi: 10.18632/oncotarget.7075. [Epub ahead of print].
36. Mathur SK, Nyenhuis SM. Changes in immune function in asthma in the elderly. *Aging Health* 2009; 5(4):551-559.
37. Busse PJ, Mathur SK. Age-related changes in immune function: effect on airway inflammation. *J Allergy Clin Immunol* 2010;126(4):690-9.
38. Murray MA, Chotirmall SH. The Impact of Immunosenescence on Pulmonary Disease. *Mediators Inflamm* 2015;2015:692546.

Table and Figures Legends

Table 1: Comparisons of all variables, measured before the treatment with Omalizumab, among the three groups with different age.

Figure 1: FEV₁ values measured before (Pre) and after (Post) Omalizumab treatment.

Comparison between Pre and Post Omalizumab treatment in subjects aged 18-39 years: p=0.002; in subjects aged 40-64 years: p=0.0001; in subjects aged ≥65 years: p=0.0001.

Comparisons among subjects with different ages: pre-values p=0.838; post-values: p=0.906

Figure 2: Asthma Control Test (AC) values measured before (Pre) and after (Post) Omalizumab treatment.

Comparison between Pre and Post Omalizumab treatment in subjects aged 18-39 years: p=0.001; in subjects aged 40-64 years: p=0.0001; in subjects aged ≥65 years: p=0.0001.

Comparisons among subjects with different ages: pre-values p=0.383; **post-values p=0.039.**

Figure 3: Prevalence of subjects with different numbers of exacerbations observed in the year before (pre) and in the last year (post) of Omalizumab treatment in the 3 groups with different ages.

Comparisons (test di Wilcoxon) of prevalence observed before and after treatment with Omalizumab: p=0.021 between pre-and post-treatment in subjects aged 18-39 years; p=0.001 between pre-and post-treatment in subjects aged 40-64 years; p=0.0001 between pre-and post-treatment in subjects aged ≥65 years

Comparisons (χ^2 test) of prevalence observed in subjects with different ages, before (p=0.898) and after (p=0.049) treatment with Omalizumab.

Figure 4: Prevalence of subjects treated with different ICS levels used before (pre) and after (post) at least 1 year of Omalizumab in the 3 groups with different ages

Low dose of ICS: <500 µg equivalent to beclometasone; Medium dose of ICS: 500-1000 µg equivalent to beclometasone; High dose of ICS: >1000 µg equivalent to beclometasone

Comparisons (test di Wilcoxon) of prevalence observed before and after treatment with Omalizumab: p=0.057 between pre-and post-treatment in subjects aged 18-39 years; p=0.0001 between pre-and post-treatment in subjects aged 40-64 years; p=0.001 between pre-and post-treatment in subjects aged ≥65 years

Comparisons (χ^2 test) of prevalence observed in subjects with different age, before (p=0.369) and after (p=0.757) treatment with Omalizumab.

Figure 5: Prevalence of subjects according to how often they used SABA (short-acting β_2 -agonists) each week as a rescue medication reported in the month before (pre) Omalizumab treatment and in the month before (post) the beginning of this study in the 3 groups with different ages.

Comparisons (test di Wilcoxon) of prevalence observed before and after treatment with Omalizumab: p=0.021 between pre-and post-treatment in subjects aged 18-39 years; p=0.0001 between pre-and post-treatment in subjects aged 40-64 years; p=0.0001 between pre-and post-treatment in subjects aged ≥65 years

Comparisons (χ^2 test) of prevalence observed in subjects with different age, .before (p=0.631) and after (p=0.641) treatment with Omalizumab

